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ENVIRONMENTAL PROTECTION AGENCY

[EPA-HQ-OPP-2007-1005; FRL-9960-77]

Chlorpyrifos; Order Denying PANNA and NRDC's Petition to Revoke Tolerances

AGENCY: Environmental Protection Agency (EPA).

ACTION: Order.

SUMMARY: In this Order, EPA denies a petition requesting that EPA revoke all tolerances for the pesticide chlorpyrifos under section 408(d) of the Federal Food, Drug, and Cosmetic Act and cancel all chlorpyrifos registrations under the Federal Insecticide, Fungicide and Rodenticide Act. The petition was filed in September 2007 by the Pesticide Action Network North America (PANNA) and the Natural Resources Defense Council (NRDC).

DATES: This Order is effective [*insert date of publication in the **Federal Register***]. Objections and requests for hearings must be received on or before [*insert date 60 days after date of publication in the **Federal Register***], and must be filed in accordance with the instructions provided in 40 CFR part 178 (see also Unit I. of the **SUPPLEMENTARY INFORMATION**.)

ADDRESSES: The docket for this action, identified by docket identification (ID) number EPA-HQ-OPP-2007-1005, is available at *http://www.regulations.gov* or at the Office of Pesticide Programs Regulatory Public Docket (OPP Docket) in the Environmental Protection Agency Docket Center (EPA/DC), West William Jefferson Clinton Bldg., Rm. 3334, 1301 Constitution Ave., NW., Washington, DC 20460-0001. The Public Reading Room is open from 8:30 a.m. to 4:30 p.m., Monday through Friday,

excluding legal holidays. The telephone number for the Public Reading Room is (202) 566-1744, and the telephone number for the OPP Docket is (703) 305-5805. Please review the visitor instructions and additional information about the docket available at *http://www.epa.gov/dockets.*

FOR FURTHER INFORMATION CONTACT: Pesticide Re-Evaluation Division (7508P), Office of Pesticide Programs, Environmental Protection Agency, 1200 Pennsylvania Ave., NW., Washington, DC 20460-0001; telephone number: (703) 347-0206; email address: *OPPChlorpyrifosInquiries@epa.gov.*

SUPPLEMENTARY INFORMATION:

I. General Information

A. Does this Action Apply to Me?

In this document EPA denies a petition by PANNA and the NRDC to revoke pesticide tolerances and cancel pesticide registrations. This action may also be of interest to agricultural producers, food manufacturers, or pesticide manufacturers. Potentially affected entities may include, but are not limited to those engaged in the following activities:

- Crop production (North American Industrial Classification System (NAICS) code 111), e.g., agricultural workers; greenhouse, nursery, and floriculture workers; farmers.
- Animal production (NAICS code 112), e.g., cattle ranchers and farmers, dairy cattle farmers, livestock farmers.
- Food manufacturing (NAICS code 311), e.g. agricultural workers; farmers; greenhouse, nursery, and floriculture workers; ranchers; pesticide applicators.

- Pesticide manufacturing (NAICS code 32532), e.g. agricultural workers; commercial applicators; farmers, greenhouse, nursery, and floriculture workers; residential users.

This listing is not intended to be exhaustive, but rather to provide a guide for readers regarding entities likely to be affected by this action. Other types of entities not listed in this unit could also be affected. The NAICS codes have been provided to assists you and others in determining whether this action might apply to certain entities. If you have any questions regarding the applicability of this action to a particular entity, consult the person listed under **FOR FURTHER INFORMATION CONTACT**.

B. How Can I Get Copies of This Document and Other Related Information?

EPA has established a docket for this action under Docket ID No. EPA-HQ-OPP-2007-1005. Additional information relevant to this action is located in the chlorpyrifos registration review docket under Docket ID No, EPA-HQ-OPP-2008-0850 and the chlorpyrifos tolerance rulemaking docket under Docket ID No, EPA-HQ-OPP-2015-0653. To access the electronic docket, go to *http://www.regulations.gov*, select "Advanced Search," then "Docket Search." Insert the docket ID number where indicated and select the "Submit" button. Follow the instructions on the regulations.gov website to view the docket index or access available documents. All documents in the docket are listed in the docket index available in regulations.gov. Although listed in the index, some information is not publicly available, e.g., Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Certain other material, such as copyrighted material, is not placed on the Internet and will be publicly available only in hard copy form. Publicly available docket materials are available in the electronic

docket or, if only available in hard copy, at the OPP Regulatory Public Docket in Rm. S-4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. The Docket Facility is open from 8:30 a.m. to 4 p.m. Monday through Friday, excluding legal holidays. The Docket Facility telephone number is (703) 305-5805.

C. Can I File an Objection or Hearing Request?

Under section 408(g) of the Federal Food, Drug and Cosmetic Act (FFDCA) (21 U.S.C. 346a(g)), any person may file an objection to any aspect of this order and may also request a hearing on those objections. You must file your objection or request a hearing on this order in accordance with the instructions provided in 40 CFR part 178. To ensure proper receipt by EPA, you must identify docket ID number EPA-HQ-OPP-2007-1005 in the subject line on the first page of your submission. All objections and requests for a hearing must be in writing, and must be received by the Hearing Clerk on or before [*insert date 60 days after date of publication in the* **Federal Register**], and may be submitted by one of the following methods:

• *Mail*:. U.S. EPA Office of Administrative Law Judges, Mailcode 1900R, 1200 Pennsylvania Ave., NW., Washington, DC 20460

• *Hand Delivery*: U.S. Environmental Protection Agency Office of Administrative Law Judges, Ronald Reagan Building, Rm. M1200, 1300 Pennsylvania Ave., NW., Washington, DC 20004. Deliveries are only accepted during the Office's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Office's telephone number is (202) 564-6255.

In addition to filing an objection or hearing request with the Hearing Clerk as

described in 40 CFR part 178, please submit a copy of the filing that does not contain CBI for inclusion in the public docket that is described in I.B.1 above. Information not marked confidential pursuant to 40 CFR part 2 may be disclosed publicly by EPA without prior notice. Submit this copy, identified by docket ID number EPA-HQ-OPP-2007-1005, by one of the following methods:

- *Federal eRulemaking Portal*: *http://www.regulations.gov*. Follow the on-line instructions for submitting comments.

- *Mail*: U.S. Environmental Protection Agency Office of Pesticide Programs (OPP) Public Regulatory Docket (7502P), 1200 Pennsylvania, Ave., NW, Washington DC 20460-0001.

- *Delivery*: OPP Regulatory Public Docket (7502P), Environmental Protection Agency, Rm. S-4400, One Potomac Yard (South Bldg.), 2777 S. Crystal Dr., Arlington, VA. Deliveries are only accepted during the Docket's normal hours of operation (8:30 a.m. to 4 p.m., Monday through Friday, excluding legal holidays). Special arrangements should be made for deliveries of boxed information. The Docket Facility telephone number is (703) 305-5805.

D. What Should be Included in Objections?

The objection stage is the second stage in the petition process under FFDCA section 408. This multi-stage process is initiated by a petition requesting establishment, modification, or revocation of a tolerance. Once EPA makes a decision on a petition, and publishes its decision in the Federal Register, the second stage of the petition process is triggered. At this point, parties who disagree with EPA's decision, whether it is a decision to grant or deny the petition, may file objections with EPA to the decision made.

The objection stage gives parties a chance to seek review of EPA's decision before the Agency. This is an opportunity for parties to contest the conclusions EPA reached and the determinations underlying those conclusions. As an administrative review stage, it is not an opportunity to raise new issues or arguments or present facts or information that were available earlier. On the other hand, parties must do more than repeat the claims in the petition. The objection stage is the opportunity to challenge EPA's decision on the petition. An objection fails on its face if it does not identify aspects of EPA's decision believed to be in error and explain the reason why EPA's decision is incorrect. This two-stage process insures that issues are fully aired before the Agency and a comprehensive record is compiled, prior to judicial review.

II. Introduction

A. What Action is the Agency Taking?

In this document, EPA denies a petition by PANNA and the NRDC. In a petition dated September 12, 2007, PANNA and NRDC (the petitioners) requested that EPA revoke all tolerances for the pesticide chlorpyrifos established under section 408 of the FFDCA. (Ref. 1) The petition also sought the cancellation of all chlorpyrifos pesticide product registrations under section 6 the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), 7 U.S.C. 136d. The PANNA and NRDC petition (the Petition) raised the following claims regarding EPA's reregistration and active registrations of chlorpyrifos in support of the request for tolerance revocation and product cancellation:

1. EPA has ignored genetic evidence of vulnerable populations.
2. EPA has needlessly delayed a decision regarding endocrine disrupting effects.
3. EPA has ignored data regarding cancer risks.

4. EPA's 2006 cumulative risk assessment (CRA) for the organophosphates misrepresented risks and failed to apply FQPA 10X safety factor. [For convenience's sake, the legal requirements regarding the additional safety margin for infants and children in section 408(b)(2)(C) of the FFDCA are referred to throughout this response as the "FQPA 10X safety factor" or simply the "FQPA safety factor." Due to Congress' focus on both pre- and post-natal toxicity, EPA has interpreted this additional safety factor as pertaining to risks to infants and children that arise due to pre-natal exposure as well as to exposure during childhood years.]

5. EPA has over-relied on registrant data.

6. EPA has failed to properly address the exporting hazard in foreign countries from chlorpyrifos.

7. EPA has failed to quantitatively incorporate data demonstrating long-lasting effects from early life exposure to chlorpyrifos in children.

8. EPA has disregarded data demonstrating that there is no evidence of a safe level of exposure during pre-birth and early life stages.

9. EPA has failed to cite or quantitatively incorporate studies and clinical reports suggesting potential adverse effects below 10% cholinesterase inhibition.

10. EPA has failed to incorporate inhalation routes of exposure.

In this order EPA is denying the Petition in full. EPA provided the petitioners with two interim responses on July 16, 2012, and July 15, 2014, respectively. The July 16, 2012, response denied claim 6 (export hazard) completely and that portion of the response was a final agency action. The remainder of the July 16, 2012, response and the July 15, 2014, response expressed EPA's intention to deny six other petition claims (1-5

and 10). [In the 2012 response, EPA did, however, inform petitioners of its approval of label mitigation (in the form of rate reductions and spray drift buffers) to reduce bystander risks, including risks from inhalation exposure, which in effect partially granted petition claim 10.] EPA made clear in both the 2012 and 2014 responses that, absent a request from petitioners, EPA's denial of those six claims would not be made final until EPA finalized its response to the entire Petition. Petitioners made no such request. EPA is finalizing its denial of those six claims in this order.

The remaining claims (7-9) all related to same issue: whether the potential exists for chlorpyrifos to cause neurodevelopmental effects in children at exposure levels below EPA's existing regulatory standard (10% cholinesterase inhibition). While these claims raised novel, highly complex and unresolved scientific issues, EPA decided it would nonetheless expedite the registration review of chlorpyrifos under FIFRA section 3(g), and attempt to address these issues several years in advance of the October 1, 2022 deadline for completing that review. Accordingly, EPA also decided as a policy matter that it would address the Petition claims raising these matters on a similar timeframe. Although EPA had expedited its registration review to address these issues, the petitioners were not satisfied with EPA's progress in responding to the Petition and they brought legal action in the 9th Circuit Court of Appeals to compel EPA to either issue an order denying the Petition or to grant the Petition by initiating the tolerance revocation process. In August 2015, the 9th Circuit issued a ruling in favor of the petitioners and ordered EPA to respond to the Petition by either denying the Petition or issuing a proposed or final rule revoking chlorpyrifos tolerances. *In re Pesticide Action Network of North America v. EPA*, 798 F.3d (9th Cir. 2015).

On November 6, 2015, pursuant to the 9th Circuit's order, EPA proposed to revoke all chlorpyrifos tolerances based in part on uncertainty surrounding the potential for chlorpyrifos to cause neurodevelopmental effects – the issue raised in petition claims 7-9. Following publication of the proposal, the 9th Circuit announced that it would retain jurisdiction over this matter and on August 12, 2016, the court further ordered EPA to complete a final petition response by March 31, 2017 and made clear that no further extensions would be granted. On November 17, 2016, EPA published a notice of data availability that released for public comment EPA's revised risk assessment that proposed a new regulatory point of departure based on the potential for chlorpyrifos to result in adverse neurodevelopmental effects.

Following a review of comments on both the November 2015 proposal and the November 2016 notice of data availability, EPA has concluded that, despite several years of study, the science addressing neurodevelopmental effects remains unresolved and that further evaluation of the science during the remaining time for completion of registration review is warranted to achieve greater certainty as to whether the potential exists for adverse neurodevelopmental effects to occur from current human exposures to chlorpyrifos. EPA has therefore concluded that it will not complete the human health portion of the registration review or any associated tolerance revocation of chlorpyrifos without first attempting to come to a clearer scientific resolution on those issues. As noted, Congress has provided that EPA must complete registration review by October 1, 2022. Because the 9th Circuit's August 12, 2016 order has made clear, however, that further extensions to the March 31, 2017 deadline for responding to the Petition would not be granted, EPA is today also denying all remaining petition claims.

B. What Is the Agency's Authority for Taking This Action?

Under section 408(d)(4) of the FFDCA, EPA is authorized to respond to a section 408(d) petition to revoke tolerance either by issuing a final rule revoking the tolerances, issuing a proposed rule, or issuing an order denying the Petition.

III. Statutory and Regulatory Background

A. FFDCA/FIFRA and Applicable Regulations

1. *In general.* EPA establishes maximum residue limits, or ''tolerances,'' for pesticide residues in food and feed commodities under section 408 of the FFDCA. Without such a tolerance or an exemption from the requirement of a tolerance, a food containing a pesticide residue is ''adulterated'' under section 402 of the FFDCA and may not be legally moved in interstate commerce. Section 408 was substantially rewritten by the Food Quality Protection Act of 1996 (FQPA) (Public Law 104–170, 110 Stat. 1489 (1996)), which established a detailed safety standard for pesticides and integrated EPA's regulation of pesticide food residues under the FFDCA with EPA's registration and re-evaluation of pesticides under FIFRA. The standard for issuing or maintaining a tolerance under section 408(b)(2)(A)(i) of the FFDCA is whether it is ''safe.'' ''Safe'' is defined by section 408(b)(2)(A)(ii) to mean that ''there is a reasonable certainty that no harm will result from aggregate exposure to the pesticide chemical residue, including all anticipated dietary exposures and all other exposures for which there is reliable information.''

While the FFDCA authorizes the establishment of legal limits for pesticide residues in food, section 3(a) of FIFRA requires the approval of pesticides prior to their

sale and distribution, and establishes a registration regime for regulating the use of pesticides. FIFRA regulates pesticide use in conjunction with its registration scheme by requiring EPA review and approval of pesticide labels and specifying that use of a pesticide inconsistent with its label is a violation of federal law. In the FQPA, Congress integrated action under the two statutes by requiring that the safety standard under the FFDCA be used as a criterion in FIFRA registration actions as to pesticide uses which result in dietary risk from residues in or on food, (*see* FIFRA section 2(bb)), and directing that EPA coordinate, to the extent practicable, revocations of tolerances with pesticide cancellations under FIFRA. (*see* FFDCA section 408(l)(1)). Under section 3(g) of FIFRA, EPA is required to re-evaluate pesticides under the FIFRA standard – which includes a determination regarding the safety of existing FFDCA tolerances – every 15 years under a program known as "registration review." The deadline for completing the registration review for chlorpyrifos is October 1, 2022.

2. *Procedures for establishing, amending, or revoking tolerances*. Tolerances are established, amended, or revoked by rulemaking under the unique procedural framework set forth in the FFDCA. Generally, a tolerance rulemaking is initiated by the party seeking to establish, amend, or revoke a tolerance by means of filing a petition with EPA. (*See* FFDCA section 408(d)(1)). EPA publishes in the **Federal Register** a notice of the petition filing and requests public comment. After reviewing the petition, and any comments received on it, section 408(d)(4) provides that EPA may issue a final rule establishing, amending, or revoking the tolerance, issue a proposed rule to do the same, or deny the petition.

Once EPA takes final action on the petition by establishing, amending, or

revoking the tolerance or denying the petition, section 408(g)(2) allows any party to file objections with EPA and seek an evidentiary hearing on those objections. Objections and hearing requests must be filed within 60 days. Section 408(g)(2)(B) provides that EPA shall "hold a public evidentiary hearing if and to the extent the Administrator determines that such a public hearing is necessary to receive factual evidence relevant to material issues of fact raised by the objections." EPA regulations make clear that hearings will only be granted where it is shown that there is "a genuine and substantial issue of fact," the requestor has identified evidence 'which "would, if established, resolve one or more of such issues in favor of the requestor," and the issue is "determinative" with regard to the relief requested. (40 CFR 178.32(b)). Further, a party may not raise issues in objections unless they were part of the petition and an objecting party must state objections to the EPA decision and not just repeat the allegations in its petition. *Corn Growers v. EPA*, 613 F.2d 266 (D.C. Cir. 2010), cert. denied, 131 S. Ct. 2931 (2011). EPA's final order on the objections is subject to judicial review. (21 U.S.C. 346a(h)(1)).

IV. Chlorpyrifos Regulatory Background

Chlorpyrifos (0,0-diethyl-0-3,5,6-trichloro-2-pyridyl phosphorothioate) is a broad-spectrum, chlorinated organophosphate (OP) insecticide that has been registered for use in the United States since 1965. By pounds of active ingredient, it is the most widely used conventional insecticide in the country. Currently registered use sites include a large variety of food crops (including tree fruits and nuts, many types of small fruits and vegetables, including vegetable seed treatments, grain/oilseed crops, and cotton, for example), and non-food use settings (e.g., ornamental and agricultural seed production, non-residential turf, industrial sites/rights of way, greenhouse and nursery production,

sod farms, pulpwood production, public health and wood protection). For some of these crops, chlorpyrifos is currently the only cost-effective choice for control of certain insect pests. In 2000, the chlorpyrifos registrants reached an agreement with EPA to voluntarily cancel all residential use products except those registered for ant and roach baits in child-resistant packaging and fire ant mound treatments.

In 2006, EPA completed FIFRA section 4 reregistration and FFDCA tolerance reassessment for chlorpyrifos and the OP class of pesticides. Having completed reregistration and tolerance reassessment, EPA is required to complete the next re-evaluation of chlorpyrifos under the FIFRA section 3(g) registration review program by October 1, 2022. Given ongoing scientific developments in the study of the OPs generally, in March 2009 EPA announced its decision to prioritize the FIFRA section 3(g) registration review of chlorpyrifos by opening a public docket and releasing a preliminary work plan to complete the chlorpyrifos registration review by 2015 – 7 years in advance of the date required by law.

The registration review of chlorpyrifos and the OPs has presented EPA with numerous novel scientific issues that the agency has taken to multiple FIFRA Scientific Advisory Panel (SAP) meetings since the completion of reregistration. [The SAP is a federal advisory committee created by section 25(d) of FIFRA, that serves as EPA's primary source of peer review for significant regulatory and policy matters involving pesticides.] Many of these complex scientific issues formed the basis of the 2007 petition filed by PANNA and NRDC and EPA therefore decided to address the Petition on a similar timeframe to EPA's expedited registration review schedule.

Although EPA expedited the chlorpyrifos registration review in an attempt to

address the novel scientific issues raised by the Petition in advance of the statutory deadline, the petitioners were dissatisfied with the pace of EPA's response efforts and have sued EPA in federal court on three separate occasions to compel a faster response to the Petition. As explained in Unit V., EPA had addressed 7 of the 10 claims asserted in the Petition by either denying the claim, issuing a preliminary denial or approving label mitigation to address the claims, but on June 10, 2015, in the *PANNA* decision, the U.S. Court of Appeals for the Ninth Circuit signaled its intent to order EPA to complete its response to the Petition and directed EPA to inform the court how – and by when – EPA intended to respond. On June 30, 2015, EPA informed the court that it intended to propose by April 15, 2016, the revocation of all chlorpyrifos tolerances in the absence of pesticide label mitigation that ensures that exposures will be safe. On August 10, 2015, the court rejected EPA's time line and issued a mandamus order directing EPA to "issue either a proposed or final revocation rule or a full and final response to the administrative Petition by October 31, 2015."

On October 30, 2015, EPA issued a proposed rule to revoke all chlorpyrifos tolerances which it published in the Federal Register on November 6, 2015 (80 FR 69080). On December 10, 2015, the Ninth Circuit issued a further order requiring EPA to complete any final rule (or petition denial) and fully respond to the Petition by December 30, 2016. On June 30, 2016, EPA sought a 6-month extension to that deadline in order to allow EPA to fully consider the most recent views of the FIFRA SAP with respect to chlorpyrifos toxicology. The FIFRA SAP report was finalized and made available for EPA consideration on July 20, 2016. (Ref. 2) On August 12, 2016, the court rejected EPA's request for a 6-month extension and ordered EPA to complete its final action by

March 31, 2017 (effectively granting EPA a three-month extension). On November 17, 2016, EPA published a notice of data availability (NODA) seeking public comment on both EPA's revised risk and water assessments and reopening the comment period on the proposal to revoke all chlorpyrifos (81 FR 81049). The comment period for the NODA closed on January 17, 2017.

V. Ruling on Petition

This order denies the Petition on the nine remaining grounds for which EPA has not issued a final denial that can be the subject of objections under section 408(g)(2) of the FFDCA. As noted in Unit II, on July 16, 2012, EPA denied as final agency action petitioners' claim 6 that the registration of chlorpyrifos created an export hazard for workers in foreign countries. That response and the response of July 15, 2014, also included EPA's preliminary denial of petition claims 1-5 and 10 (except to the extent EPA granted that claim) and EPA's responses to those claims are now incorporated into this order as set forth below. This unit also includes EPA's basis for denying petition claims 7-9. Each specific petition claim is summarized in this Unit V. immediately prior to EPA's response to the claim.

1. Genetic Evidence of Vulnerable Populations

a. Petitioners' claim. Petitioners claim that as part of EPA's reregistration decision (which was completed in 2006 with the completion of the organophosphate cumulative risk assessment) the Agency failed to calculate an appropriate intra-species uncertainty factor (i.e., within human variability) for chlorpyrifos in both its aggregate and cumulative risk assessments (CRA). They assert that certain relevant, robust data, specifically the Furlong et al. (2006) study (Ref. 3) that addresses intra-species variability

in the behavior of the detoxifying enzyme paraoxonase (PON1), indicate that the Agency should have applied an intra-species safety factor "of at least 150X in the aggregate and cumulative assessments" rather than the 10X factor EPA applied. Petitioners conclude by noting that applying an intra-species factor of 100X or higher would require setting tolerances below the level of detection, which therefore should compel EPA to revoke all chlorpyrifos tolerances.

b. *Agency Response.* Petitioners are correct that the Agency, as part of the 2006 OP CRA, evaluated, but did not rely on Furlong et al. in setting the intra-species uncertainty factor for that assessment. The Agency did not rely on the results of the PON1 data in the OP CRA because these data do not take into consideration the complexity of OP metabolism, which involves multiple metabolic enzymes, not just PON1. In addition, EPA believes the methodology utilized in the Furlong et al. study to measure intra-species variability – i.e., combining values from multiple species (transgenic mice and human) to determine the range of sensitivity within a single species – is not consistent with well-established international risk assessment practices. Further, EPA believes that petitioners' assertion that the Furlong et al. study supports an intra-species uncertainty factor of at least 150X is based on an analysis of the data that is inconsistent with EPA policy and widely- accepted international guidance on the development of intra-species uncertainty factors. In addition, the 2008 FIFRA SAP did not support the use of the Furlong et al (2006) study alone in deriving an intra-species factor. For these reasons, and as further explained below, EPA believes it is not appropriate to solely rely on the results of the Furlong et al. study, or petitioners' interpretation of those results, for purposes of determining the intra-species uncertainty

factor. To determine that factor, EPA first uses science tools to quantitatively characterize human variability in both exposure and dosimetry, and then determines the appropriate intra-species uncertainty factor to protect sensitive populations. Specifically, for chlorpyrifos, EPA uses a physiologically-based pharmacokinetic (PBPK) model to account for human variability in the absorption, distribution, metabolism and excretion (ADME) of chemicals based on key physiological, biochemicals, and physicochemical determinants of these ADME processes, including the influence of PON1 variability.

Addressing human variability and sensitive populations is an important aspect of the Agency's risk assessment process. The Agency is well aware of the issue of PON1 and has examined the scientific evidence on this source of genetic variability. PON1 is one of the key detoxification enzymes of chlorpyrifos and is included as part of the PBPK model used by EPA in the 2014 human health risk assessment (HHRA) and 2016 revised risk assessment. Specifically, PON1 is an A-esterase which can metabolize chlorpyrifos-oxon without inactivating the enzyme. (Ref. 4) Indeed, as part of the 2008 SAP, EPA performed a literature review of PON1 and its possible use in informing the intra-species (i.e., within human variability) uncertainty factor. This literature review can be found in the draft Appendix E: Data Derived Extrapolation Factor Analysis to the draft Science Issue Paper: Chlorpyrifos Hazard and Dose Response Characterization.(Ref. 5) In sum, the Agency considered available PON1 data from more than 25 studies from diverse human populations worldwide.

The Agency focused on the PON1-192 polymorphism since it has been linked to chlorpyrifos-oxon sensitivity in experimental toxicology studies and, has been evaluated in epidemiology studies attempting to associate PON1 status with health outcomes

following OP pesticide exposure in adults and children (Holland et al., 2006; Chen et al., 2003. (Ref. 6). [Note, Holland et al (2006) and Furlong et al (2006) report findings from the same cohort. The Holland reference provides enzymes activities for specific polymorphisms in Table 4; the Furlong paper does not report such values and provides information primarily in graphical form.] However, EPA believes that focusing on PON1 variability in isolation from other metabolic action is not an appropriate approach for developing a data-driven uncertainty factor. The Agency solicited feedback from the SAP on the utility of the PON1 data, by itself, for use in risk assessment; the SAP was similarly not supportive of using such data in isolation. Specifically, the SAP report states:

> *"...the information on PON1 polymorphisms should not be used as the sole factor in a data-derived uncertainty factor for two main reasons: 1) it is only one enzyme in a complex pathway, and is subsequent to the bioactivation reaction; therefore it can only function on the amount of bioactivation product (i.e., chlorpyrifos-oxon) that is delivered to it by CYP450); and 2) the genotype of PON1 alone is insufficient to predict vulnerability because the overall level of enzyme activity is ultimately what determines detoxification potential from that pathway; thus, it is better to use PON1 status because it provides information regarding PON1 genotype and activity. Some of the data from laboratory animal studies in PON knockout animals are using an unrealistic animal model and frequently very high dose levels, and do not reflect what might happen in humans."* (Ref. 7)

Based on a detailed review of the literature and the comments from the SAP, the Agency has determined that such data are not appropriate for use alone in deriving an intra-species uncertainty factor for use in human health risk assessment. As indicated by the SAP report, multiple factors (e.g., other enzymes such as P450s, carboxylesterases, butyrylcholinesterase) are likely to impact potential population sensitivity, rendering the results of the PON1 data, by themselves, insufficiently reliable to support a regulatory

conclusion about the potential variation of human sensitivity to chlorpyrifos.

Since the 2008 SAP, several epidemiological studies have been published that considered the association between PON status/genotype and health outcome. Hofmann et al. (2009) recently reported associations between PON1 status and inhibition of butyrylcholinesterase (BuChE) in a group of pesticide handlers in Washington. The authors note that this study requires replication with larger sample size(s) and more blood samples. (Ref. 8) Given the limitations of Hofmann et al., the Agency has not drawn any conclusions from this study. The Q/R-192 and/or C/T -108 polymorphism at the promoter site have been evaluated recently as a factor affecting birth or neurobehavioral outcomes following gestational exposure to OPs. (Refs. 9, 10, 11) These studies (Eskanazi., et al., 2010 (Ref. 9); Harley et al., 2011 (Ref. 10); Engel et al., 2011 (Ref. 11)) were evaluated by EPA in preparation for the April 2012 SAP review.

Petitioners further emphasize that the Furlong et al. study supports an intra-species uncertainty factor of over 164X given the range of variability seen in that study. The 164X value is derived from sensitivity observed in transgenic mice expressing human PON1Q-192 compared with mice expressing human PON1R-192 combined with the range of plasma arylesterase (AREase) from the newborn with the lowest PON1 level compared with the mother with the highest PON1 level from a group of 130 maternal-newborn pairs from the CHAMACOS (Center for the Health Assessment of Mothers and Children of Salinas) cohort.

EPA believes it is fundamentally at odds with international risk assessment practices to combine values from both mouse and human data to determine the potential

range of variability within a single species – regardless of whether the test animals express a human PON1 enzyme. As the 2008 FIFRA SAP explained, PON1 is but a single enzyme that should not be considered in isolation to predict the overall level of enzyme activity that may affect human sensitivity to a substance. Using a 164X intra-species uncertainty factor derived from the Furlong et al. study would take this practice one step further by relying upon combined PON1 values from different species with differing overall metabolic activity to derive the intra-species factor. EPA does not believe this approach is an appropriate means of determining the potential range of intra-species variability.

Finally, petitioners' assertion that the Furlong study supports an intra-species uncertainty factor of at least 150X is based on an analysis of that study that is inconsistent with EPA policy and widely- accepted international guidance on the development of intra-species uncertainty factors. In deriving the intra-species uncertainty factor in its risk assessments, EPA is guided by the principles of the 2005 IPCS (Ref. 12) guidance on chemical specific adjustment factors (CSAFs) and the EPA's 2014 Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation. (Ref. 13) These guidances recommend that intra-species factors should be extrapolated from a measure of central tendency in the population to a measure in the sensitive population (i.e., to extrapolate from a typical human to a sensitive human). To base the factor on the difference between the single lowest and highest measurements in a given study, as petitioners suggest in this instance, would likely greatly exaggerate potential intra-species variability. That approach effectively assumes that the point of departure in an EPA risk assessment will be derived

from the least sensitive test subject, thereby necessitating the application of an intra-species factor that accounts for the full range of sensitivity across a species. Since EPA does not develop its PoDs in this fashion; the approach suggested by petitioners is not appropriate.

In summary, the Agency has carefully considered the issue of PON1 variability and determined that data addressing PON1 in isolation are not appropriate for use alone in deriving an intra-species uncertainty factor and that the issue is more appropriately handled using a PBPK model. Further, the derivation of the 164X value advocated by the petitioners is based on combining values from humanized mice with human measured values with a range from highest to lowest; the Furlong et al. derivation is inappropriate and inconsistent with international risk assessment practice. (Ref. 2) The 2008 FIFRA SAP did not support the PON1 data used in isolation. Finally, petitioners' statement that the Furlong et al. study supports an intra-species uncertainty factor of at least 150X likely overstates potential variability. EPA therefore denies this aspect of the Petition.

2. *Endocrine Disrupting Effects*

a. Petitioners' claim. Petitioners summarize a number of studies evaluating the effects of chlorpyrifos on the endocrine system, asserting that, taken together, the studies "suggest that chlorpyrifos may be an endocrine disrupting chemical, capable of interfering with multiple hormones controlling reproduction and neurodevelopment." The petitioners then assert that EPA should not have delayed consideration of endocrine effects absent finalization of the Endocrine Disruptor Screening Program (EDSP) (Ref. 14) and should have quantitatively incorporated the studies into the chlorpyrifos IRED.

b. Agency Response. This portion of the Petition appears largely to be a complaint

about the completeness of EPA's reregistration decision and a request that EPA undertake quantitative incorporation of endocrine endpoints into its assessment of chlorpyrifos. The Petition does not explain whether and how endocrine effects should form the basis of a decision to revoke tolerances. The basis for seeking revocation of a tolerance is a showing that the pesticide is not "safe." Petitioners have neither asserted that EPA should revoke tolerances because effects on the endocrine system render the tolerances unsafe, nor have petitioners submitted a factual analysis demonstrating that aggregate exposure to chlorpyrifos presents an unsafe risk to humans based on effects on the endocrine system. Rather, the Petition appears to collect a number of studies suggesting that chlorpyrifos may have effects on the endocrine system and that EPA should have considered those health impacts at reregistration in a quantitative assessment.

To the extent that petitioners are seeking tolerance revocation on these grounds, the Petition fails to provide a sufficient basis for revocation because, in addition to the preceding defects, the cited data do not provide quantitative data (i.e. endpoints/points of departure) that indicate endocrine effects at doses that are more sensitive than the points of departure used in the chlorpyrifos risk assessment that are based on cholinesterase inhibition. While the cited studies provide qualitative information that exposure to chlorpyrifos may be associated with effects on the androgen and thyroid hormonal pathways, these data alone do not demonstrate that current human exposures from existing tolerances are unsafe. The Agency noted similar effects during its evaluation of information submitted by People for the Ethical Treatment of Animals (PETA) and the Physicians Committee for Responsible Medicine (PCRM) during its review of existing information as part of EPA's EDSP, as discussed below. Based on the review of that

data, EPA concluded that the effects seen in those studies do not call into question EPA's prior safety determinations supporting the existing tolerances; the data do not indicate a risk warranting regulatory action, and the petitioners have provided no specific information to alter this determination.

Consequently, the Petition does not support a conclusion that existing tolerances are unsafe due to potential endocrine effects. This portion of the Petition is therefore denied.

As petitioners may be aware, since the filing of the petition, EPA has completed the evaluation of chlorpyrifos under EPA's EDSP, as required under FFDCA section 408(p) that confirms EPA's conclusions. On April 15, 2009, a **Federal Register** notice was published in which chlorpyrifos was included in the initial list of chemicals (List 1) to receive EDSP Tier 1 test orders. The EDSP program is a two-tiered screening and testing program, Tier 1 and Tier 2 tests. Tier 1 includes 11 assays in the battery; these data are intended to allow EPA to determine whether certain substances (including pesticide active and other ingredients) have the potential to interact with the endocrine system and cause an effect in humans or wildlife similar to an effect produced by a "naturally occurring estrogen, or other such endocrine effects as the Administrator may designate." The purpose of Tier 2 tests is to identify and establish a quantitative, dose-response relationship for any adverse effects that might result from the interactions with the endocrine system.

On November 5, 2009, EPA issued Tier 1 test orders to the registrants of chlorpyrifos, requiring a battery of 11 screening assays to identify the potential to interact with the estrogen, androgen, or thyroid hormonal systems. (Ref. 15)

The agency received and reviewed all 11 EDSP Tier 1 screening assays for chlorpyrifos. On June 29, 2015, the agency completed the EDSP weight of evidence (WoE) conclusions for the Tier 1 screening assays for List 1 chemicals, including chlorpyrifos. In addition to the Tier 1 data, the WoE evaluations considered other scientifically relevant information (OSRI), including general toxicity data and open literature studies of sufficient quality. In determining whether chlorpyrifos interacts with the estrogen, androgen or thyroid pathways, the agency considered the number and type of effects induced, the magnitude and pattern of responses observed across studies, taxa, and sexes. Additionally, the agency also considered the conditions under which effects occurred, in particular whether or not endocrine-related responses occurred at dose(s) that also resulted in general systemic or overt toxicity. The agency concluded that, based on weight of evidence considerations, EDSP Tier 2 testing is not recommended for chlorpyrifos since there was no evidence of potential interaction with the estrogen, androgen and thyroid pathways. The EDSP Tier 1 WoE assessment and associated data evaluation records for chlorpyrifos are available online. (Ref. 16) This assessment further supports EPA's denial of this portion of the Petition.

3. Cancer Risks

a. Petitioners' claim. Petitioners claim that the Agency "ignored" a December 2004 National Institutes of Health Agricultural Health Study (AHS) by Lee et al. (2004) (Ref. 17) that evaluated the association between chlorpyrifos and lung cancer incidence. (Ref. 17) The petition summarizes the results of the AHS study, stating that the incidence of lung cancer has a statistically significant association with chlorpyrifos exposure. The Petition then asserts that these data are highly relevant and therefore should have been

referenced in the final aggregate assessment for chlorpyrifos or the OP CRA. Petitioners do not otherwise explain whether and how these data support the revocation of tolerances or the cancellation of pesticide registrations.

b. Agency Response. As explained in the previous section, the basis for seeking revocation of a tolerance is a showing that the pesticide is not "safe." Claiming that EPA failed to reference certain data in its risk assessment regarding carcinogenicity does not amount to illustrating that the tolerances are unsafe. To show a lack of safety, petitioners would have to present some fact-based argument demonstrating that aggregate exposure to chlorpyrifos poses an unsafe carcinogenic risk. Petitioners have not presented such an analysis. Accordingly, EPA is denying the Petition to revoke chlorpyrifos tolerances or cancel chlorpyrifos registrations to the extent the Petition relies on claims pertaining to carcinogenicity.

Despite the inadequacy of petitioners' cancer claims, in the course of the Agency's review of chlorpyrifos, EPA has examined the Lee et al. study cited by petitioners (Ref. 17) among other lines of evidence. EPA has concluded that the Lee et al. investigation does not alter the Agency's weight of evidence determination concerning chlorpyrifos' carcinogenic potential, and therefore does not alter the Agency's current cancer classification for chlorpyrifos. Specifically, the Agency does not believe this evidence raises sufficient grounds for concern regarding chlorpyrifos that EPA should consider initiating action based upon this information that might lead to revocation of the chlorpyrifos tolerances or cancellation of the chlorpyrifos registrations.

The Agency was aware of the December 2004 study cited by petitioners. While Lee et al. observed a possible association between chlorpyrifos use and the incidence of

lung cancer, the authors also stressed that further evaluation was necessary before concluding the association was causal in nature.(Ref. 17) Additional evaluation is necessary because of possible alternative explanations for the Lee et al. study, which include unmeasured confounding factors or confounding factors not fully accounted for in the analysis, and possible false positive results due to the performance of multiple statistical tests.

EPA has been a collaborating agency with the AHS since 1993, and continues to closely monitor the AHS literature. The Agency is working closely with the AHS researchers to clearly understand the results of their research efforts to ensure the Agency appropriately interprets these data as future studies are published. Between 2003 and 2009 there have been six nested case-control analyses within the AHS which evaluated the use of a number of agricultural pesticides, including chlorpyrifos, in association with specific anatomical cancer sites, in addition to the previously published cohort study (Ref. 17) cited by the petitioners. As noted below, both the Agency and Health Canada have comprehensively reviewed these data.

In accordance with the Agency's 2005 Guideline for Cancer Risk Assessment (Ref. 18), chlorpyrifos is classified as "Not Likely to be Carcinogenic to Humans" based on the lack of evidence of carcinogenicity in male or female mice and male or female rats. In chronic toxicity/ carcinogenicity studies, animals received chlorpyrifos in their feed every day of their lives (78 weeks for mice and 104 weeks for rats) at doses thousands of times greater than any anticipated exposure to humans from authorized uses. There was no evidence of cancer in the experimental animal studies. Additionally, available evidence from *in vivo* and *in vitro* assays did not support a mutagenic or

genotoxic potential of chlorpyrifos.

Recently, the Agency conducted its own review of the six nested case-control analyses and one cohort study within the AHS concerning the carcinogenic potential of chlorpyrifos. (Ref. 19) EPA concluded with respect to the AHS lung cancer results that the findings are useful for generating hypotheses, but require confirmation in future studies. This conclusion is consistent with that of researchers from Health Canada. Specifically, Weichenthal et al. (2010) (Ref. 20) published a review article in Environmental Health Perspectives on pesticide exposure and cancer incidence in the AHS cohort. Their review of these same studies concluded that the weight of experimental toxicological evidence does not suggest that chlorpyrifos is carcinogenic, and that epidemiologic results currently available from the AHS are inconsistent, lack replication, and lack a coherent biologically plausible carcinogenic mode of action. The authors did note positive exposure-response associations for chlorpyrifos and lung cancer in two separate evaluations.

In summary, while there is initial suggestive epidemiological evidence of an association between chlorpyrifos and lung cancer to only form a hypothesis as to a carcinogenic mode of action, additional research (including follow-up AHS research) is needed to test the hypothesis. Consequently, at this time it is reasonable to conclude chlorpyrifos is not a carcinogen in view of the lack of carcinogenicity in the rodent bioassays and the lack of a genotoxic or mutagenic potential. The Agency concludes that existing epidemiological data (including Lee et al.) do not change the current weight of the evidence conclusions. The Agency continues to believe there is not a sufficient basis to alter its assessment of chlorpyrifos as not likely to be carcinogenic to humans when

multiple lines of evidence are considered (e.g., epidemiology findings, rodent bioassay, genotoxicity); therefore, chlorpyrifos cancer risk would not be a factor in any potential Agency risk determination to revoke tolerances for chlorpyrifos.

4. CRA misrepresents risks, failed to apply FQPA10X Safety Factor

a. Petitioners' claim. Petitioners assert that EPA relied on limited data and inaccurate interpretations of data to support its decision to remove the FQPA safety factor in the 2006 OP CRA. Specifically, the petitioners challenge the Agency's use of data from a paper by Zheng et al. (2000) (Ref. 21) claiming that, in contrast to the Agency's analysis of the study data, the data does show an obvious difference between juvenile and adult responses to chlorpyrifos. Petitioners conclude by asserting that the Zheng et al. study supports using a 10X safety factor for chlorpyrifos in the CRA.

b. Agency Response. Petitioners' assertions do not provide a sufficient basis for revoking chlorpyrifos tolerances. As explained previously, the ground for seeking revocation of a tolerance is a showing that the pesticide is not "safe." The petitioners' claim that the data EPA relied upon support a different FQPA safety factor for chlorpyrifos in the CRA does not amount to a showing that chlorpyrifos tolerances are unsafe. To show a lack of safety, petitioners would have to present a factual analysis demonstrating that the lack of a 10X safety factor in the CRA for chlorpyrifos poses unsafe cumulative exposures to the OPs. Petitioners have not made such a showing. For this reason, EPA is denying the petitioners' request to revoke chlorpyrifos tolerances or cancel chlorpyrifos registrations to the extent that request relies on claims pertaining to EPA's failure to provide a 10X safety factor in the 2006 CRA based on the results of the Zheng et al. study.

Despite the inadequacy of petitioners' FQPA safety factor claims, EPA examined the evidence cited by petitioners for the purpose of evaluating whether the evidence raises sufficient grounds for concern regarding chlorpyrifos that EPA should consider initiating the actions sought by the petitioners.

In general, when the Agency conducts a cumulative assessment, the scope of cumulative risk is limited to the common mechanism endpoint -- which in this case of the 2006 OP CRA, was cholinesterase inhibition, the primary toxicity mode of action for the OPs. As such, for the OP CRA, experimental toxicology data on AChE inhibition were used for developing relative potency estimates, points of departure, and informing the FQPA safety factor used in the OP CRA. EPA relied on brain AChE data from adult female rats dosed for 21 days or longer for estimating relative potency and points of departure. At approximately three weeks of oral exposure to OPs, AChE inhibition reaches steady state in the adult rat such that continued dosing does not result in increased inhibition. This timeframe of toxicity (21-days and longer) was selected as there was high confidence in the potency estimates derived from the steady state toxicology studies due to the stability of the AChE inhibition.

The Agency's 2006 OP CRA contained EPA's complete FQPA safety factor analysis, (Ref. 22) which involved consideration of pre-natal and post-natal experimental toxicology studies, in addition to exposure infc[rma]tion. In the OP CRA, pre-natal exposure AChE studies in rats show that the fetus is no more sensitive than the dam to AChE inhibition and the fetus is often less sensitive than the dam. Thus, evaluating the potential for increased toxicity of juveniles from post-natal exposure was a key

component in determining the magnitude of the FQPA safety factors in the OP CRA. Furthermore, because characteristics of children are directly accounted for in the cumulative exposure assessment, the Agency's methods did not underestimate exposure to OPs.

In the 2006 OP CRA, each OP was assigned a 10X FQPA safety factor unless chemical-specific AChE data on young animals were available to generate a data derived safety factor. To best match the relative potency factor (RPF)s and PODs based on repeated dosing, the Agency used repeated dosing data in juveniles for developing the FQPA safety factors. For chlorpyrifos, at the time of the 2006 OP CRA, the only such data available were from the Zheng et al. literature study.

The petitioners are correct that Dr. Carey Pope of Oklahoma State University provided the Agency with the raw data from the Zheng et al. study. These raw data were used to develop the plot in the 2006 OP CRA which was reproduced in the Petition. Petitioners accurately note that for other OPs a benchmark dose modeling approach was used and that no BMD values were reported for chlorpyrifos. In determining the FQPA safety factor, petitioners claim that the Agency misinterpreted the brain AChE data from Zheng et al.

As shown in the plot reproduced on page 15 of the Petition, the dose-response data in the Zheng et al. study are variable and lack a monotonic shape at the low dose end of the dose response curve. The Agency acknowledges that at the high dose, the pups appear to be more sensitive. However, at the low dose end of the response curve, relevant for human exposures and, thus, the cumulative risk assessment (i.e., at or near the 10% inhibition level), little to no difference is observed. Therefore, despite the lack

of BMD estimates for the Zheng et al. study, the Agency is confident in the value used to address the common mechanism endpoint (AChE inhibition) addressed in the 2006 CRA. Since that time, the Agency attempted BMD modeling of the Zheng et al. data as part of the 2011 preliminary chlorpyrifos HHRA (Ref. 23) which yielded low confidence results due to the variability in the data.

Dow AgroSciences submitted a comparative cholinesterase study (CCA) for chlorpyrifos. CCA studies are specially designed studies to compare the dose-response relationship in juvenile and adult rats. This CCA study includes two components: 1) acute, single dosing in post-natal day 11 and young adult rats and 2) 11-days of repeating dosing in rat pups from PND11-21 and 11-days of repeated dosing in adult rats. The CCA study for chlorpyrifos is considered by EPA to be high quality and well-designed. The preliminary risk assessment for chlorpyrifos' reports BMD estimates from this CCA study. Specifically, for the repeated dosing portion of the study, the BMD_{10s} of 0.80 (0.69 $BMDL_{10}$) and 1.0 (0.95 $BMDL_{10}$) mg/kg/day respectively for female pups and adults support the FQPA safety factor of 1X for the AChE inhibition endpoint used in the 2006 OP CRA. As such, petitioners' claims regarding the CRA and FQPA safety factor is denied.

5. Over-reliance on registrant data.

a. Petitioners' claims. Petitioners assert that in reregistering chlorpyrifos EPA "cherry picked" data, "ignoring robust, peer-reviewed data in favor of weak, industry-sponsored data to determine that chlorpyrifos could be re-registered and food tolerances be retained." As such, the Agency's reassessment decision is not scientifically defensible.

b. Agency response. This portion of the Petition does not purport to be an independent basis for revoking chlorpyrifos tolerances or cancelling chlorpyrifos registrations. Rather, this claim appears to underlie petitioners' arguments in other sections of the Petition. While petitioners claim that EPA ignored robust, peer-reviewed data in favor of weak, industry-sponsored data for the reregistration of chlorpyrifos, petitioners do not cite to any studies other than those used to support their other claims. In general, petitioners did not provide any studies in the Petition that EPA failed to evaluate. Since the specific studies cited by petitioners are not associated with this claim, but rather their other claims, EPA's response to the specific studies are, therefore, addressed in its responses to petitioners' other claims. However, EPA explains below why, as a general matter, the Agency does not believe it "over-relied" on registrant data in evaluating the risks of chlorpyrifos in its 2006 reregistration decision.

In spite of petitioners' claim, the Agency does not ignore robust, peer-reviewed data in favor of industry-sponsored data. Further, EPA has a very public and well-documented set of procedures that it applies to the use and significance accorded all data utilized to inform risk management decisions. Registrant generated data, in response to FIFRA and FFDCA requirements, are conducted and evaluated in accordance with a series of internationally harmonized and scientifically peer-reviewed study protocols designed to maintain a high standard of scientific quality and reproducibility. (Refs. 23 and 24).

Additionally, to further inform the Agency's risk assessment, EPA is committed to the consideration of other sources of information such as data identified in the open, peer-reviewed literature and information submitted by the public as part of the regulatory

evaluation of a pesticide. An important issue, when evaluating any study, is its scientific soundness and quality, and thus, the level of confidence in the study findings to contribute to the risk assessment.

The literature was searched, fully considered, and provided additional information on, chlorpyrifos mode of action, pharmacokinetics, epidemiology, neurobehavioral effects in laboratory animals, and age dependent sensitivity to cholinesterase inhibition.

Therefore, by evaluating registrant data in accordance with internationally harmonized and scientifically peer-reviewed study protocols, undertaking thorough open literature searches, and considering information provided by the public, the Agency is confident that its assessment for chlorpyrifos in 2006 was reasonably based upon the best available science at the time of the assessment. Previous sections of this response to petitioners' claims regarding the Agency's inadequate use of various data only further highlights and supports the scientifically defensible results of the Agency's assessment. Petitioners' claim that the Agency overly relies on registrant data is therefore denied.

6. EPA has failed to properly address the exporting hazard in foreign countries from chlorpyrifos.

As noted in Unit II., in EPA's July 16, 2012 interim petition response EPA issued a final denial of this claim. That denial constituted final agency action and EPA is not reopening consideration of that claim.

7.-9. EPA failed to quantitatively incorporate data demonstrating long-lasting effects from early life exposure to chlorpyrifos in children; EPA disregarded data demonstrating that there is no evidence of a safe level of exposure during pre-birth and early life stages; EPA failed to cite or quantitatively incorporate studies and clinical

reports suggesting potential adverse effects below 10% cholinesterase inhibition.

a. *Petitioners' claims.* The petitioners assert that human epidemiology and rodent developmental neurotoxicity data suggest that pre-natal and early life exposure to chlorpyrifos can result in long-lasting, possibly permanent damage to the nervous system and that these effects are likely occurring at exposure levels below 10% cholinesterase inhibition, EPA's existing regulatory standard for chlorpyrifos and other OPs. They assert that EPA has therefore used the wrong endpoint as a basis for regulation and that, taking into account the full spectrum of toxicity, chlorpyrifos does not meet the FFDCA safety standard or the FIFRA standard for registration.

b. Agency response. EPA has grouped claims 7-9 together because they fundamentally all raise the same issue: whether the potential exists for chlorpyrifos to cause neurodevelopmental effects in infants and children from exposures (either to mothers during pregnancy or directly to infants and children) that are lower than those resulting in 10% cholinesterase inhibition – the basis for EPA's long-standing point of departure in regulating chlorpyrifos and other OPs. While petitioners may perhaps disagree, unlike the claims addressed above, these claims were not truly challenges to EPA's 2006 reregistration decision for chlorpyrifos, but rather, challenges to EPA's ongoing approval of chlorpyrifos under FIFRA and the FFDCA that rely in large measure on data published after EPA completed both its 2001 chlorpyrifos Interim Reregistration Decision and the 2006 OP CRA that concluded the reregistration process for chlorpyrifos and all other OPs. As matters that largely came to light after the completion of reregistration, these petition issues are issues to be addressed as part of the registration review of chlorpyrifos – the next round of re-evaluation under section 3(g) of FIFRA. As

petitioners are aware, past EPA administrations prioritized the registration review of the OPs in no small measure to begin to focus on the question of OP neurodevelopmental toxicity, which was, and remains, an issue at the cutting edge of science, involving significant uncertainties. EPA has three times presented approaches and proposals to the FIFRA SAP for evaluating recent epidemiologic data (some of which is cited in the Petition) exploring the possible connection between *in utero* and early childhood exposure to chlorpyrifos and adverse neurodevelopmental effects. The SAP's reports have rendered numerous recommendations for additional study and sometimes conflicting advice for how EPA should consider (or not consider) the epidemiology data in conducting EPA's registration review human health risk assessment for chlorpyrifos. While industry and public interest groups on both sides of this issue can debate what the recommendations mean and which recommendations should be followed, one thing should be clear to all persons following this issue: the science on this question is not resolved and would likely benefit from additional inquiry.

EPA has, however, been unable to persuade the 9th Circuit Court of Appeals that further inquiry into this area of unsettled science should delay EPA's response to the Petition. Faced with an order requiring EPA to respond to the Petition, in October 2015, EPA chose to issue a proposed rule to revoke all chlorpyrifos tolerances based in part on the uncertain science surrounding neurodevelopmental toxicity suggested by certain epidemiology studies. The comments EPA has received on that proposal and on EPA's November 17, 2016 NODA suggest that there continue to be considerable areas of uncertainty with regard to what the epidemiology data show and deep disagreement over how those data should be considered in EPA's risk assessment.

Although not a legal consideration, it is important to recognize that for many decades chlorpyrifos has been and remains one of the most widely used pesticides in the United States, making any decision to retain or remove this pesticide from the market an extremely significant policy choice. In light of the significance of this decision and in light of the significant uncertainty that exists regarding the potential for chlorpyrifos to cause adverse neurodevelopmental effects, EPA's preference is to fully explore approaches raised by the SAP and commenters on the proposed rule, and possibly seek additional authoritative peer review of EPA's risk assessment prior to finalizing any regulatory action in the course of registration review. As the 9th Circuit has made clear in its August 12, 2016 order in *PANNA v. EPA*, EPA must provide a final response to the Petition by March 31, 2017, regardless of whether the science remains unsettled and irrespective of whatever options may exist for more a complete resolution of these issues during the registration review process.

While EPA acknowledges its obligation to respond to the Petition as required by the court, the court's order does not and cannot compel EPA to complete the registration review of chlorpyrifos in advance of the October 1, 2022 deadline provided in section 3(g) of FIFRA, 7 U.S.C. 136a(g). Although past EPA administrations had chosen to attempt to complete that review several years in advance of the statutory deadline (and respond to the Petition on the same time frame), it has turned out that it is not possible to fully address these issues early in the registration review period. As a result, EPA has concluded that it should alter its priorities and adjust the schedule for chlorpyrifos so that it can complete its review of the science addressing neurodevelopmental effects prior to making a final registration review decision whether to retain, limit or remove

chlorpyrifos from the market. Accordingly, EPA is denying these Petition claims and intends to complete a full and appropriate review of the neurodevelopmental data before either finalizing the proposed rule of October 30, 2015, or taking an alternative regulatory path.

EPA's denial of the Petition on the grounds provided above is wholly consistent with governing law. The petition provision in FFDCA section 408(d) does not address the timing for responding to this petition nor does it limit the extent to which EPA may coordinate its petition responses with the registration review provisions of FIFRA section 3(g). Further, provided EPA completes registration review by October 1, 2022, Congress otherwise gave the EPA Administrator the discretion to determine the schedule and timing for completing the review of the approximately over 1000 pesticide active ingredients currently subject to evaluation under section 3(g). EPA may lawfully re-prioritize the registration review schedule developed by earlier administrations provided that decision is consistent with law and an appropriate exercise of discretion. *See Federal Communications Commission v. Fox Television Stations*, 129 S.Ct. 1800 (2009) (Administrative Procedure Act does not require that a policy change be justified by reasons more substantial than those required to adopt a policy in the first instance). Nothing in FIFRA section 3(g) precludes EPA from altering a previously established registration review schedule. Given the absence of a clear statutory directive, FIFRA and the FFDCA provide EPA with discretion to take into account EPA's registration review of a pesticide in determining how and when the Agency responds to FFDCA petitions to revoke tolerances. As outlined above, given the importance of this matter and the fact that critical questions remain regarding the significance of the data

addressing neurodevelopmental effects, EPA believes there is good reason to extend the registration review of chlorpyrifos and therefore to deny the Petition. To find otherwise would effectively give petitioners under the FFDCA the authority to re-order scheduling decisions regarding the FIFRA registration review process that Congress has vested in the Administrator.

10. Inhalation Exposure from Volatilization

a. Petitioners' claim. Petitioners assert that when EPA completed its 2006 OP CRA, EPA failed to consider and incorporate significant exposures to chlorpyrifos-contaminated air that exist for some populations in communities where chlorpyrifos is applied. Petitioners assert that these exposures exceeded safe levels when considering cholinesterase inhibition as a point of departure and that developmental neurotoxicity may occur at even lower exposure levels than those resulting in cholinesterase inhibition.

b. Agency response. To the extent petitioners are asserting that human exposure to chlorpyrifos spray drift and volatilized chlorpyrifos present neurodevelopmental risks for infants and children, EPA is denying this claim for the reasons stated above in our response to claims 7-9. As noted, EPA believes that, given the uncertainties associated with this identified risk concern, the appropriate course of action is for EPA to deny the Petition and work to further resolve this area of unsettled science in the time remaining for the completion of registration review under section 3(g) of FIFRA.

With respect to petitioners' claim that exposures to spray drift and volatilized chlorpyrifos present a risk from cholinesterase inhibition, EPA is denying the Petition for the reasons previously identified in EPA's Spray Drift Mitigation Decision of July 16, 2012 [EPA-HQ-OPP-2008-0850] and EPA's interim response of July 15, 2014 [EPA-

HQ-OPP-2007-1005] addressing chlorpyrifos volatilization. In the Spray Drift Mitigation Decision, EPA determined that the chlorpyrifos registrants' adoption of label mitigation (in the form of label use rate reductions and no spray buffer zones) eliminated risk from cholinesterase inhibition as a result of spray drift. As for risks presented by volatilized chlorpyrifos that may occur following application, EPA's July 15, 2014 interim response to the Petition explained that recent vapor phase inhalation studies for both chlorpyrifos and chlorpyrifos-oxon made clear that neither vapor phase chlorpyrifos nor chlorpyrifos-oxon presents a risk of cholinesterase inhibition. Specifically, those studies, as indicated in EPA's memorandum, *Chlorpyrifos: Reevaluation of the Potential Risks from Volatilization in Consideration of Chlorpyrifos Parent and Oxon Vapor Inhalation Toxicity Studies* (Ref. 25), revealed that levels of chlorpyrifos and chlorpyrifos-oxon in vapor form are much lower than the levels seen in earlier aerosol studies that are better suited for evaluating spray drift. Indeed, no cholinesterase inhibition was observed in either volatility study. What is clear from these data is that the air cannot hold levels of volatilized chlorpyrifos or its oxon that are capable of causing adverse effects from cholinesterase inhibition.

VI. Regulatory Assessment Requirements

As indicated previously, this action announces the Agency's order denying a petition filed, in part, under section 408(d) of FFDCA. As such, this action is an adjudication and not a rule. The regulatory assessment requirements applicable to rulemaking do not, therefore, apply to this action.

VII. Submission to Congress and the Comptroller General

The Congressional Review Act, 5 U.S.C. 801 *et seq.*, does not apply because this

action is not a rule for purposes of 5 U.S.C. 804(3).

IX. References

The following is a listing of the documents that are specifically referenced in this document. The docket includes these documents and other information considered by EPA, including documents that are referenced within the documents that are included in the docket, even if the referenced document is not physically located in the docket. For assistance in locating these other documents, please consult the technical person listed under FOR FURTHER INFORMATION CONTACT.

1. The Petition from NRDC and PANNA and EPA's various responses to it are available in docket number EPA-HQ-OPP-2007-1005 available at *http://www.regulations.gov*.

2. FIFRA Scientific Advisory Panel (2016). "Chlorpyrifos: Analysis of Biomonitoring Data". Available at: *https://www.epa.gov/sap/meeting-materials-april-19-21-2016-scientific-advisory-panel*.

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7. U.S. EPA (2008). Transmittal of Meeting Minutes of the FIFRA Scientific Advisory Panel Meeting Held September 16-18, 2008 on the Agency's Evaluation of the Toxicity Profile of Chlorpyrifos. Available at *http://www.epa.gov/scipoly/sap/meetings/2008/september/sap0908report.pdf* at 61.

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14. For additional information on the Endocrine Disruptor Screening program see ***http://www.epa.gov/endo/.***

15. For information related to the status of EDSP test orders/DCIs, status of EDSP OSRI: order recipient submissions and EPA responses, and other EDSP assay information see http://www.epa.gov/endo/pubs/toresources/index.htm.

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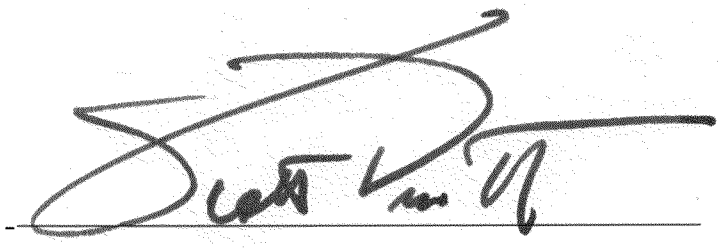
Authority: 7 U.S.C. 136 *et seq.* and 21 U.S.C. 346a.

Dated: 3/29/2017.



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